REMARKS

Claim Amendments

Claims 39, 40 and 119-125 are amended to recite "consisting of a sequence" or "consists of a sequence" rather than "comprising a sequence" or "comprises a sequence." Claims 39 and 40 are amended to recite "an isolated oligonucleotide." The specification supports these amendments throughout, for example, by teaching, "For each mutation, discriminating oligonucleotides that contained the mutated base at the 3' end were designed." Specification at page 20, lines 31-32. Claims 39, 40, and 119-125 are also amended to recite SEQ ID NO: 1 in place of "a human mitochondrial genome." Support for this amendment can be found in the specification at page 8, lines 18-20, which teaches, "Mitochondrial mutations are determined with reference to wild-type human mitochondrial sequence. Sequence information can be found at the website gen.emory.edu/mitomap.html and at SEQ ID NO:1." No new matter is added.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 39, 40, and 119-125 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

The Office Action asserts that the previous amendment to correct the designation of the mutation represents new matter. Office Action at page 2, lines 21-22. Applicants disagree in view of the obvious nature of the error in designating the mutation and the obvious correction thereof.

Two elements are necessary to correct an error within the specification. (1)

"Determination that the skilled practitioner would recognize the existence of error" and (2) "Determination that the skilled practitioner would recognize the appropriate correction." Office Action at page 3, lines 9-12; *In re* Oda, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971). Each element will be discussed in turn.

Determination that the skilled practitioner would recognize the existence of error

The claims recite an isolated oligonucleotide probe consisting of a sequence of at least 12 contiguous nucleotides of SEQ ID NO:1, wherein the oligonucleotide probe comprises a ΔC mutation at nucleotide 303. When a skilled artisan interprets this claim, he must interpret it by comparing it to a wild-type reference sequence, *e.g.*, SEQ ID NO: 1 (the human mitochondrial genome). Without a wild-type reference sequence, a ΔC mutation at nucleotide 303 is uninterpretable. The specification clearly states, "Mitochondrial mutations are determined with reference to wild-type human mitochondrial sequence. Sequence information can be found at the website gen.emory.edu/mitomap.html and at SEQ ID NO: 1." Specification at page 8, lines 18-20. The specification also teaches on page 12, lines 4-6, "Mutations can first be identified by comparison to sequences present in public databases for human mitochondrial DNA, *e.g.*, at gen.emory.edu/mitomap.html and at SEQ ID NO: 1." Thus, in order to identify the disclosed mitochondrial mutations, the specification has provided the reader, a skilled artisan, with the reference wild-type human mitochondrial sequence.

The specification originally taught that there was a ΔC mutation at nucleotide 302. This original teaching cannot, however, be interpreted in view of the wild-type reference sequence provided by the specification. Position 302 in the wild-type sequence (SEQ ID NO: 1) contains an adenosine (A). One of skill in the art would understand that

you cannot delete a C from a position where an A resides. Therefore, the skilled practitioner would recognize an error since he would clearly recognize that a ΔC mutation could not occur at nucleotide 302.

This assertion is confirmed by Dr. Anirban Maitra, a skilled practitioner in the art of human genetics. In his accompanying Declaration he states that the error would have been obvious to him and those of skill in the art. See para. 4.

Determination that the skilled practitioner would recognize the appropriate correction

Located directly adjacent to nucleotide position 302 in SEQ ID NO: 1 is a homopolymeric tract of cytosines commonly referred to in the art as D310. Marchington *et al.* teaches, "[t]he D310 tract consists of a run of 12-18 C:Gs, with a T:A near the middle at bp 310." *Am. J. Hum. Genet.* 1997:60, 408-416, at page 410, left hand column, lines 9-10 and Figure 1A; Exhibit 1. One of ordinary skill in the art would know that DNA polymerases commonly "slip" when they encounter a run of identical nucleotides, such as the D310 homopolymeric C-tract. Appelmelk and Vandenbroucke-Grauls teach, in a physiology and genetics textbook:

> On replication, DNA slippage (slipped-strand mispairing) in C-tracts may give rise to daughter DNA that is either one C shorter or longer; this can occur at very high (1%) frequencies.

Helicobacter pylori Physiology and Genetics. Online textbook. Chapter VI, 35, at page 3, lines 29-31; Exhibit 2. Further, Marchington (*supra*) teaches, "length variation [of D310] is presumably caused by replication slippage." Exhibit 1 at page 413, lines 14-15. Once one of skill in the art had identified the erroneous teaching of a ΔC mutation at nucleotide 302, he would have looked at the adjacent D310 homopolymeric C-tract.

Because it is well known that DNA polymerases commonly "slip" during replication of C-tracts, often causing deletions, the skilled artisan would have surely recognized that the correct and intended teaching was a ΔC mutation at the immediately adjacent C-tract, *i.e.*, at nucleotide 303. Thus, the skilled practitioner would have recognized the appropriate correction of the error.

This assertion is confirmed by Dr. Anirban Maitra in his Declaration. See para. 5.

Furthermore, two post-filing date publications co-authored by one of the inventors of the instant application confirm the error and the correction. The first publication teaches:

> Remarkably, the remaining seven tumors showed deletions or insertions in a mononucleotide repeat sequence (CCCC..CCCTCCCCCC) between nucleotides 303 and 316-318 (inside the D-loop). For easier designation, we will refer to this region as D310, a term coined previously by other investigators (18) [referring to Marchington *et al.*, Exhibit 1].

Sanchez-Cespedes *et al.*, *Cancer Research* 2001:61, 7015-7019, page 7016, left hand column, lines 37-41; Exhibit 3 (emphasis added). The second publication teaches:

> Although alterations may occur throughout the mitochondrial genome, the C-tract (between nucleotides 303 and 315) located in the D loop of the mitochondrial genome has emerged as a locus of increased polymorphism in the general population and mutation in primary tumors.

Ha *et al. Clinical Cancer Research* 2002:8, 2260-2265, page 2260, left hand column, lines 8-13; Exhibit 4 (emphasis added). Thus, one of skilled in the art would have correctly identified the error and the correction.

The skilled practitioner would have recognized an error within the specification after realizing that a ΔC mutation could not occur at a position occupied by an A in the

wild-type sequence. The skilled practitioner would have also recognized the correction of the error after seeing the immediately adjacent deletion-prone C-tract beginning at nucleotide 303. Therefore, the amendments do not add new matter in view of the obvious nature of the error and the obvious correction thereof.

Applicants respectfully request withdrawal of the rejection.

Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 39, 40, and 119-125 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Genbank Accession No. U25391. Applicants respectfully traverse the rejection.

The Office Action asserts that the 715 base pair "Genbank Accession No. U25391 comprises more than 30 contiguous nucleotides of the mitochondrial genome identical to the delta 302 C [the mutation is actually delta 303 C] deletion of SEQ ID NO: 1." Office Action at page 7, lines 2-4.

Amended independent claims 39 and 40 recite an isolated oligonucleotide probe, or primer consisting of a sequence of at least 12 contiguous nucleotides of SEQ ID NO: 1. A sequence alignment[1] reveals that there are 25 mismatches between Genbank Accession No. U25391 and SEQ ID NO:1. Exhibit 5, at page 2. Thus, the 715 base pair U25391 sequence does not anticipate the amended claims because it does not consist of at least 12 contiguous nucleotides of the recited sequence. It contains other sequences as well.

Applicants respectfully request withdrawal of the rejection.

[1] ClustalW sequence alignment of nucleotides 1-1260 of SEQ ID NO:1 and Genbank Accession U25391. ebi.ac.uk/clustalw/

Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 39, 40, and 119-124 are rejected under 35 U.S.C. § 102(b) as being anticipated by NEB catalog (1998/1999), pp. 121, 284. Applicants traverse the rejection.

The Office Action asserts that "the NEB catalog offered for sale a random primer mix of both 12 and 24 nucleotide primers." Office Action at page 7, lines 7-8. The Office Action then meticulously discusses a calculation, which reveals, "3.2 x 10^8 of every 12-mer and about 9 molecules of every single 24 mer are present in each tube of the 12 and 24 nucleotide mixtures, respectively." Office Action at page 7, lines 7-10.

To advance prosecution, applicants have amended the claims to recite "an isolated oligonucleotide" primer or probe having a particular recited sequence. The random primer mixtures are not isolated primers or probes having a particular sequence as claimed. Thus, the random primer mixtures of the NEB catalog do not anticipate the claims as amended.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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Enclosures